

Tivicay

Summary

Tivicay is the name given to a pill containing the anti-HIV drug dolutegravir. Although Tivicay is generally well-tolerated, general side effects are uncommon and can include nausea, vomiting, diarrhea, headache and difficulty falling asleep. These are usually temporary and mild. Tivicay is taken as part of combination treatment with other anti-HIV drugs, once or twice daily. Tivicay can be taken day or night, with or without food.

What is Tivicay?

Tivicay is the name of a pill that contains the anti-HIV drug dolutegravir. This drug belongs to a group or class of drugs called integrase inhibitors

Tivicay is used with other anti-HIV drugs as part of combination treatment for HIV infection. Your doctor will tell you how often you need to take Tivicay – either once or twice daily.

How does Tivicay work?

When HIV infects a cell, it takes control of that cell. HIV then forces the cell to make many more copies of the virus. To make these copies, the cell uses proteins called enzymes. When the activity of these enzymes is reduced, the production of HIV slows to a very low level.

Tivicay interferes with enzymes needed by HIV, including an enzyme called integrase. This enzyme is used by HIV-infected cells to make more copies of HIV.

Since Tivicay in combination with other medicines can inhibit, or reduce, the activity of these enzymes, Tivicay-containing treatment causes HIV-infected cells to slow down or stop producing new viruses.

How do people with HIV use Tivicay?

Tivicay is used together with other anti-HIV drugs. Such combinations are called antiretroviral therapy, or ART. For more information on ART, see CATIE's *Your Guide to HIV Treatment*.

For many people with HIV, the use of ART has increased their CD4+ cell counts and decreased the amount of HIV in their blood (viral load). These beneficial

FACT SHEET

**Published
2021**

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effects help to greatly reduce the risk of developing a life-threatening infection. Neither Tivicay nor any other anti-HIV medication is a cure for HIV. It is therefore important that you see your doctor for checkups and lab tests on a regular basis.

Evidence shows that HIV-positive people who are on ART, engaged in care, and have an ongoing undetectable viral load are substantially less likely to transmit HIV to others, be it through sex, when sharing equipment to use drugs or during pregnancy and birth. In fact, the evidence for sexual transmission shows that people on ART who maintain an undetectable viral load do not pass HIV to their sexual partners. For further information see the CATIE fact sheet *HIV treatment and an undetectable viral load to prevent HIV transmission*. However, it is still a good idea to use condoms because they can reduce your risk for getting and passing on other sexually transmitted infections.

Warnings

Pregnancy

In May 2018, regulatory agencies issued cautionary statements because dolutegravir was associated with an apparent risk of birth defects in a clinical trial in the southern African country of Botswana. Specifically, HIV-positive women who used dolutegravir at the time of conception appeared to have a small but increased risk of giving birth to infants with a type of birth defect called a neural tube defect. This risk was greater than seen when women used other anti-HIV treatments.

However, long-term data have not shown an increased risk of birth defects associated with the use of dolutegravir-containing regimens outside of Botswana, including other African countries and in Canada. Furthermore, the number of children born with such birth defects in Botswana to women who used dolutegravir was limited. Also, over the course of several years in the same study, the risk of giving birth to an infant with a birth defect fell among women who used dolutegravir at the time of conception.

The good news is that the latest data from Botswana indicate the level of birth defects in infants born to women who use dolutegravir at the

time of conception is now very low and similar to that seen in women who use other anti-HIV drugs at the time of conception.

If you are taking Tivicay and are pregnant or want to have a baby, let your doctor know.

Side effects

1. General

Tivicay is usually well-tolerated. However, like many medicines, Tivicay can be associated with these symptoms:

- nausea
- vomiting
- diarrhea
- headache
- abdominal discomfort/pain

If these persist or are bothersome tell your doctor right away.

2. Weight gain

Some studies with HIV-positive people who used dolutegravir as part of combination treatment found that weight gain occurred. In some people the increased weight gain was modest – a few kilos – while in others it was more substantial. Research suggests that some HIV-positive people with the following features or characteristics tend to gain weight when on ART:

- women
- people of African, Black or Caribbean descent
- people whose CD4+ cell count fell below the 200 cell/mm³ level at some point in the past.

However, some HIV-positive people without these features can also gain weight. The cause of increased weight in HIV-positive people is not clear because studies suggest that HIV-negative people of the same age and gender are also generally gaining weight even though they are not taking ART.

An increase of one or two kilograms in weight over the course of one year is normal when initiating

ART and is what has been reported in clinical trials in the current era. However, should you gain more than this amount of weight, speak to your nurse or doctor so that your weight gain can be assessed. Doctors and nurses also take into account a person's waist size and/or body mass index (BMI) – this is a number derived by dividing their height by the square of their weight. If your nurse or doctor has found that your BMI is increasing and is outside what is considered healthy then they will investigate possible causes for an increase in weight.

There may be one or more reasons that your BMI is increasing, including the following:

Physical activity – Are you getting enough daily physical activity, including walking and climbing stairs? If not, can you begin a program of exercise? Speak to your nurse or doctor about what kind of exercise is right for you.

Sleeping problems – Rest and sleep quality are sometimes overlooked aspects of health. A large observational study in HIV-negative people found that people who have sleeping problems tend to gain weight. If you are unexpectedly gaining weight, speak to your doctor or nurse to rule out any sleep problems.

Emotional and mental health – Are there factors in your life that can affect how you respond to stressful events? For instance, when stressed, some people eat more fat and carbohydrate-rich foods as a source of comfort. Repeated engagement in excessive intake of carbohydrates and fatty foods can lead to weight gain over time. Depression can affect appetite—some people gain weight, others lose weight. If you notice weight gain along with changes in your mood, speak to your doctor or nurse.

Metabolic conditions, hormones and arthritis

Some conditions and life-stages are associated with weight gain, including the following:

- pre-diabetes and diabetes
- problems with the thyroid gland and its hormones

- being post-menopausal
- arthritis

Diet

Not everyone follows a diet that is informed by dietary guidelines. If you have access to subsidized dietary counselling (sometimes this is provided in large hospitals and clinics), you may benefit from consulting a registered dietitian. Registered dietitians can assess the quality and quantity of meals, and if necessary, provide helpful advice about making healthy changes.

Substance use

Alcohol contains calories. Is excess consumption of alcohol an issue for you? Excess consumption of alcoholic beverages could suggest unaddressed mental health and emotional issues.

Prescription medicines

Some prescription medicines (for conditions other than HIV) have the potential to cause changes in weight, particularly increased weight. It can be useful to speak to a pharmacist about all the medicines that you are taking to see if any are associated with changes in weight. You can then discuss any medicines that your pharmacist has identified with your doctor.

Bear in mind

While the above list covers some potential causes of weight gain in HIV-positive people, it is not exhaustive.

3. Emotional issues— Anxiety and depression

Note that *all* integrase inhibitors, including dolutegravir, have been associated with rare cases of anxiety and depression. Whether these drugs caused anxiety or depression is not clear. In some reports, the rare cases of anxiety and/or depression associated with the use of integrase inhibitors occurred mainly in people who had a history of these issues.

Anxiety and depression are relatively common in HIV-positive people (regardless of whether they are on treatment or the type of treatment that they take). If you are taking dolutegravir and think that you may have developed anxiety or depression, speak to your doctor right away. Your doctor can help determine if you have anxiety or depression and if there is any relationship between them and the medicines that you are taking.

Symptoms of anxiety and depression can include the following:

- becoming easily upset or angry
- feeling fearful
- excessive worry
- unexpected feelings of sadness
- prolonged feelings of sadness, anger or depression
- feeling hopeless
- loss of pleasure in everyday activities
- unexpectedly feeling tired or a lack of energy
- difficulty falling asleep, staying asleep or waking up prematurely
- strange thoughts

If you have any of these feelings, contact your doctor or nurse.

If you have thoughts of harming yourself or others, dial 911 right away.

4. Older people

Tivicay has not been studied in large numbers of people aged 65 or older. Older people may have major organ systems (heart, liver, kidneys and so on) that do not work as well as in healthy younger people. Older people may also be taking multiple medicines that have the potential to interact with Tivicay. The manufacturer therefore advises doctors that in people aged 65 or older Tivicay should be used with caution.

5. Liver

The manufacturer (ViiV) states that patients who also have hepatitis B and/or C virus may be at increased risk for liver injury. ViiV recommends that doctors monitor the health of the liver in patients who take Tivicay.

6. The kidneys

The kidneys filter the blood and then put waste materials into urine and reabsorb nutrients and other useful materials back into the blood.

People who have a significant degree of kidney injury do not have sufficiently high levels of dolutegravir in their blood. Specifically, the manufacturer recommends that Tivicay **not** be used by people whose kidneys are not functioning normally. That is, people whose eGFR (estimated glomerular filtration rate) is less than 30 mL/min should not use Tivicay.

Uncommon side effects

Side effects that were *rare* (less than 1%) in clinical trials included the following:

- feeling sleepy in the day time
- muscle weakness
- muscle pain

Drug interactions

In general, integrase inhibitors such as dolutegravir (in Tivicay) tend not to interfere with many other drugs (raising or lowering their levels in the blood). Dolutegravir causes few interactions with other drugs. However, there are other medicines that interfere with dolutegravir levels in the blood, usually decreasing them. Below are some drug interactions; this list is not exhaustive. Always speak to your pharmacist and doctor about your HIV treatment and its potential for interactions with other medicines and/or herbs or supplements that you are taking.

Here are recommendations from the manufacturer about potentially significant drug interactions with dolutegravir (in Tivicay):

Other HIV drugs

Etravirine (Intelence) – this drug can reduce the concentration of dolutegravir in the blood. Therefore, the manufacturer recommends that dolutegravir should not be used with etravirine unless it is also taken with one of the following combinations of drugs:

- atazanavir (Reyataz) + ritonavir (Norvir)
- darunavir (Prezista) + ritonavir (Norvir)
- lopinavir + ritonavir (in Kaletra)

Nevirapine (Viramune) – dolutegravir should not be used with nevirapine, as there is not enough information to make dosing recommendations.

Acid-reducing agents, laxatives, metal supplements and buffered medicines

Dolutegravir should be taken 2 hours before or 6 hours after taking these medicines.

Examples of acid-reducing agents include:

- Alka-Seltzer
- Gaviscon (tablets and syrup)
- Maalox (liquid and tablets)
- Milk of Magnesia
- Pepto-Bismol and Pepto Bismol Children's
- Roloids
- Tums

Metal supplements include those containing iron, calcium and magnesium. Viiv's advice for these supplements is as follows:

“When taken with food, Tivicay and calcium and/or iron supplements or multivitamins containing calcium and/or iron can be taken at the same time.” If you are taking Tivicay on an empty stomach, it “should be taken two hours before or six hours after taking supplements containing calcium and/or iron.”

Multiple sclerosis (MS) treatments

Viiv recommends that Tivicay not be used in people who are taking the drug fampridine (also known as dalfampridine) as Tivicay may cause increased concentrations of this drug in the body, leading to side effects.

Abnormal heart rhythm drugs

The drug dofetilide (Tikosyn) is prescribed to treat abnormal heart rhythms. Dolutegravir can raise levels of dofetilide. Although dofetilide is not approved in Canada, many Canadians travel to the U.S., where it is approved, and may be prescribed this medicine. The manufacturer warns that dofetilide should never be used by patients who are taking dolutegravir, as high concentrations of dofetilide can occur causing serious injury.

Anti-seizure drugs

Oxcarbazepine, carbamazepine (Tegretol), phenobarbital, phenytoin (Dilantin) – dolutegravir should not be used with these drugs as there is not enough information to make dosing recommendations.

Antibiotics

Rifampin – this drug reduces the concentration of dolutegravir in the blood. The manufacturer recommends that dolutegravir should be used at a dose of 50 mg twice daily if rifampin must also be taken. However, the manufacturer also notes that in the case of patients who have used integrase inhibitors in the past and who have HIV that may be or is suspected to be resistant to integrase inhibitors, doctors and nurses should seek alternative antibiotics to rifampin where possible.

Diabetes drugs

Metformin – as dolutegravir can raise levels of metformin in the blood, the manufacturer recommends close monitoring of patients when they are starting or stopping therapy with dolutegravir. The manufacturer also suggests that it may be necessary to reduce the dose of metformin in some dolutegravir users.

Herbs

St. John's wort (or compounds found in St. John's wort such as hypericin, hyperforin) can significantly reduce dolutegravir levels and this herb should not be used. Although St. John's wort is the only herb listed here, note that other herbs are likely to interact with dolutegravir.

Resistance and cross-resistance

Over time, as new copies of HIV are made in the body, the virus changes its structure. These changes, called mutations, can cause HIV to resist the effects of anti-HIV drugs, which means those drugs will no longer work for you.

To reduce the risk of developing drug resistance, all anti-HIV drugs should be taken every day exactly as prescribed and directed. If doses are delayed, missed or not taken as prescribed, the level of medicines in the blood may fall too low. If this happens, the HIV in your body can become resistant to the medication. If you find you are having problems taking your medications as directed, speak to your doctor, nurse or pharmacist about this. They can find ways to help you.

When HIV becomes resistant to one drug in a class, it sometimes becomes resistant to other drugs in that class. This is called cross-resistance. Feel free to talk with your doctor about your current and future treatment options. To help you decide what these future options might be, at some point your doctor can have a small sample of your blood analyzed to test for resistance. Should the HIV in your body become resistant to dolutegravir, your doctor can recommend a new treatment combination for you.

For patients whose integrase inhibitor regimens are failing, doctors can request laboratory testing of their blood to assess the degree of resistance to integrase inhibitors. This will help doctors determine whether or not an integrase inhibitor can be used in future regimens.

Dosage

Tivicay is available in tablets of different strengths. Your doctor will tell you the dose of Tivicay that is right for you. ViiV recommends that in people

who have HIV that is resistant to other integrase inhibitors, Tivicay needs to be taken twice daily.

If you miss a dose, the manufacturer recommends that you take it "as soon as you remember, but if your next dose is due within four hours, skip the dose you missed and take your next one at the usual time. Then continue your treatment as before."

If you continue to miss doses, speak to your doctor, nurse or pharmacist about ways of helping you stick to a regular schedule of pill-taking.

Availability

Tivicay is licensed in Canada for the treatment of HIV infection. Your doctor or pharmacist can tell you more about the availability and coverage of Tivicay in your region. CATIE's online module *Federal, Provincial and Territorial Drug Access Programs* also contains information about Canadian drug coverage.

References

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Disclaimer

Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.

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Production of this document has been made possible through a financial contribution from the Public Health Agency of Canada. The views expressed herein do not necessarily represent the views of the Public Health Agency of Canada.

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